19. A method according to claim 13 wherein the mutant herpes simplex virus has been modified within the BamH1 restriction fragment of the long terminal repeat of the viral genome.

20. A method according to claim 19, wherein the modification is a deletion of from 0.1 to 3 kb of the BamH1 restriction fragment of the long terminal repeat of the viral genome.

B'

21. A method according to claim 20 wherein the deletion is from 0.7 to 0.8 kb.

22. A method according to claim 13 wherein the mutant herpes simplex virus is strain 1716.--

REMARKS

Reconsideration is requested.

Claims 1-12 have been canceled, without prejudice. New claims 13-22 are pending. Support for the amended claims may be found throughout the specification and no new matter has been added. The specification has been amended to include the deposit information of Strain 1716 and a copy of the Deposit Certificate is attached.

The Section 101 rejection of claims 1-10 is moot in view of the above. The claims have been amended to recite statutorily protectable subject matter.

The Section 112, first paragraph, rejection of claims 1-12 is moot in view of the above. The claims are submitted to be supported by an enabling disclosure and the Examiner is requested to consider the following in this regard.

The Examiner is of the opinion that the specification "does not reasonably provide enablement for a composition comprising any and all mutant herpes simplex virus having a modified gamma 34.5 gene to treat any and all non-neuronal cancers in any and all mammal... by delivering an effective amount of the same composition through any and all routes of administration to the mammal." See, page 3 of the Office Action dated August 15, 2000.

In response, the applicants submit that the teachings provided by the present application represent a generally-applicable approach – that is, that HSV mutants in which the gamma 34.5 gene is mutated so as to be non-functional are effective in the treatment of non-neuronal cancers.

The Examiner is urged to appreciate that in In re DeGeorge, the court held that the standard for enablement under 35 USC § 112, first paragraph, is whether one of ordinary skill in the art would be able to use the description of the application to make and use the claimed invention. "An inventor need not, however, explain every detail, since he is speaking to those skilled in the art" (DeGeorge v. Benier, 226 USPQ 758, 762 (Fed. Cir. 1985)). The applicants submit that, on account of the generalized teaching of the present application, it would be incommensurate with the scope of the invention to require that the present applicants limit the claims to precise mutant variants, precise treatment conditions, precise types of cancer, and precise species of animal. Since the teachings of the invention can be applied to many different situations, with markedly successful results in each case, it would be impossible to specify in the application every possible permutation of these factors in a specific manner as seemingly required by the Examiner. The Examiner must appreciate that the specification and claims are directed to the ordinarily skilled artisan and that the specification is not required to be a detailed operators manual. Rather, the ordinarily skilled artisan must have been able to make and use the claimed invention from the teaching of the application, without undue experimentation. The applicants believe they have provided an enabling specification. To require that the claims be

limited specifically to the particular embodiments described in the examples of the application, i.e. the use of HSV 1716 in treating human or murine mesotheliomas or melanomas, would result in a scope of protection far narrower than the broad range of indications in which the ordinarily skilled person could reap the benefits of the present invention.

In particular, the applicants submit that it would be entirely reasonable for the ordinarily skilled artisan to expect, for example, all ICP34.5 null HSV mutants to act in the same way as HSV1716. All wild-type HSV strains have an RL1 gene encoding ICP34.5; the genes are collinear, and the coding capacity is the same in each case. Inactivation of ICP34.5 results in a virus which is a virulent but which is selectively replication-competent in tumor cells. There is no reason to expect that there will be strain variation and the applicants submit that, in fact, this would be unexpected.

As for the Examiner's concern regarding the range of tumors which may be treated, the applicants urge the Examiner to appreciate that melanoma and mesothelioma, which were both demonstrated to be effectively treated in the present application, are entirely distinct types of tumor. Melanoma is a cancer of the skin, while mesothelioma is a cancer of the lung. Melanoma arises from melanocytes and mesothelioma from the mesothelium of the lung. Thus, the cell types, the progression of the tumor, and the affected organs are quite different in these two types of cancer. Hence, the fact that effective treatment of both of these types of cancer has been demonstrated in the present application would indicate to the ordinarily skilled person that other non-neuronal cancers would likewise be treatable in the same way. Furthermore, the applicants have since shown that HSV1716 can selectively kill ovarian cancer cells; medulloblastoma tumors and teratocarcinoma (see, e.g. Kesari, S., *et al.* (1995). "A mutant herpes simplex virus replicates in brain tumors but not in neurons derived from a human embryonal carcinoma cell line." *Laboratory Investigation* 73, 636-648 (of record); Lasner, T.M.,

et al. (1996). "Herpes simplex virus type 1 (HSV1) mutants for the treatment of childhood brain tumours." *Journal of Neuropathology and Experimental Neurology* 55, 1259-1269; Kucharczuk, J.C., *et al.* (1997). "Use of a 'replication restricted' herpes virus to treat experimental human malignant mesothelioma." Cancer *Research,* 57:466-471; and Randazzo, B.P., *et al* .(1997). "Treatment of experimental subcutaneous human melanoma with a replication restricted herpes simplex virus mutant." *Journal of Investigative Dermatology,* 108, 933-937). Thus, the applicants submit that it would be reasonable to presume that the results taught in the present application could have been validly and reliably extrapolated to a wide range of different situations in which non-neuronal tumors arise, without undue experimentation.

Following on from this point, the applicants also submit that it would have been entirely reasonable to assume that effective treatment in mice can generally be extrapolated to humans. Indeed, the specific examples of the present invention, on pages 8 et seq. of the application, describe the effect of HSV 1716 on the *in vitro* growth of human malignant mesothelioma cell line (REN), on the *in vivo* growth of such cells in the peritoneal cavity of SCID mice, and on the *in vivo* growth of experimental human malignant melanoma outside the CNS. Positive results were observed in all three sets of studies, indicating that the virus was effective in both human and murine models. Thus the ordinarily skilled person is clearly taught that the general teachings of the present invention are not merely limited to one particular animal model, but are more widely applicable.

As far as the mode of administration of the virus in the methods of treatment of the present invention is concerned, the applicants have demonstrated success both with direct intratumoral injection in a number of locations, and with injection of the virus into the peritoneum rather than directly into the tumor (see, e.g., Kucharczuk, J.C.). The applicants submit that there was no reason to believe that other, alternative methods which are commonly

used in the art for the administration of a virus, would not have also been suitable in the present treatment methods. The applicants submit that it would be unfair to require the applicants to limit the claims to cover only intratumoral injection, when the principles of the present invention are clearly more generally applicable. It is not the mode of administration of the virus which is important in the context of the present application, but rather the surprising and significant finding that gamma 34.5 null HSV mutants can be used in the treatment of non-neuronal cancers. This is the subject of the present claims, and the administration of such viruses by intratumoral injection is merely a preferred embodiment of the general teaching.

In summary, the applicants submit that the skilled person is provided with a generally-applicable principle which is pertinent not only in relation to the specific embodiments described in the examples of the present application, but also to other, comparable situations. The applicants are therefore of the opinion that the claims are not unduly broad, in view of the relevance of the invention to many different indications and the generally advance level of skill in this art.

The Section 112, first paragraph, rejection of claim 10 is moot in view of the above.

As noted above and in the attached, Strain 1716 has been deposited under the provisions of the Budapest Treaty. Moreover, the applicants submit that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the Depository.

The Section 112, second paragraph, rejection of claims 1-12 is moot in view of the above. The amended claims are submitted to be definite and in compliance with Section 112, second paragraph.

Specifically, the applicants respectfully submit the phrase "non-neuronal cancer" is not ambiguous or indefinite. It is clearly stated in the specification that "non-neuronal" means that

the location of the tumor is "outside the brain and nervous system" (see, for example, page 6, lines 15 and 16, "non-neuronal e.g. non-CNS location in the patients' body", page 6, line 26). As is described in the introductory paragraph of the specification, the field of the invention is exemplified by mesotheliomas, melanoma, ovarian carcinoma and bladder cancer. On page 6, lines 16-22, the specification teaches that the tumor may be metastatic i.e., wherein the cancer cells originate elsewhere, or they may be primary tumors. Moreover, the applicants confirm that "deletion of" in the now-canceled claim 8 refers to a deletion of 0.1 to 3 kb of the BamH1 "s" fragment in the long terminal repeat. The amended claims refers to "of the BamH1 restriction fragment of the long terminal repeat of the viral genome" for clarity.

The Section 112, second paragraph, rejection of claims 11 and 12 for allegedly omitting essential elements, is moot in view of the above. The claims have been rewritten with the Examiner's comments in mind.

The Section 102 rejection of claims 1-10 and 12 over MacLean (Journal of General Virology 72:631-639, 1991) or Brown (WO 92/13943) are moot in view of the above. Similarly, the Section 102 rejection of claims 1-5, 7-8 and 12 over Taha (Journal of Virology 70:705-716, 1989); the Section 102 rejection of claims 1-8 and 12 over Chou (Science 250:1262-1266, 1990) or Markert (Neurosurgery 32:597-603 1993); and the Section 102 rejection of claims 1-12 over Randazzo (Virology 211:94-101, 1995) are moot in view of the above.

Moreover, the Randazzo et al. document cited by the Examiner under Section 102(a) against claims 1-12, is not citable against the present application as this report is the applicants' own work. See, the attached Declaration.

The pending claims are submitted to be patentable over the cited art.

The Examiner is requested to hold in abeyance the provisional Section 102 rejection of claim 11 over copending Application No. 08/776,350, until the claims are found allowable.

Similarly, the Examiner is requested to hold in abeyance the provisional rejection of claim 11 as being obvious in view of claims 43-58 of the copending Application No. 08/776,350 until an indication of allowable claims is made.

The Examiner is requested return a further initialed copy of the PTO 1449 Form bearing the OIPE date stamp of July 24, 2000, as the initialed copy of the same which was forwarded with the Office Action of August 15, 2000, fails to include the Examiner's initials next to U.S. Patent Nos. 4,859,587 and 5,328,688. The applicants assume that as the Examiner has initialed the entirety of the PTO 1449 Form that all of the cited references have been considered.

In view of the above and attached, the claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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By: _____

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

BROWN et al

Serial No. 09/117,218

Filed: January 11, 1999

For: TREATMENT OF NON-NEURONAL CANCER USING HSV MUTANT

Atty. Ref.: 620-70

Group: 1632

Examiner: Nguyen, Q

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Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION

We, Susanne M. Brown, Alasdair R. Maclean, Nigel W. Fraser, and Bruce P. Randazzo, do hereby declare and say as follows:

1. Together with Santosh Kesari, Richard M. Gesser, David Alsop and John C. Ford, we are joint authors of a paper entitled "Treatment of Experimental Intracranial Murine Melanoma with Neuroattenuated Herpes Simplex Virus 1 Mutant" appearing in Virology 211, 84-101 (1995), which was published after May 10, 1995.

2. We are aware of, and have reviewed U.S. patent Application No. 09/117,218, and the Office Action of August 15, 2000, issued therein.

3. We confirm that we, along with Steven Albelda, Larry Kaiser and John Kucharczuk, are the sole inventors of the subject matter claimed in Application No. 09/117,218. The other named joint authors, Santosh Kesari, Richard M. Gesser, David Alsop and John C. Ford, of the above-identified publication performed useful, practical work such as would justify them being

named as a joint authors of a journal article, but they did not contribute inventively to the invention described and claimed in U.S. patent Application No. 09/117,218.

We do hereby declare that all statements made herein of our own knowledge are true and that all statements made on information belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application and any patent issuing thereon.

Further, declarants sayeth not.

Susanne M. Brown — Date 11/12/00

Alasdair R. Macrae — Date 14/12/00

Nigel W. Fraser — Date 11/12/00

Bruce P. Randazzo — Date 12/12/00

PHLS Public Health Laboratory Service

Centre for Applied Microbiology and Research

This document certifies that Virus Strain
(Deposit ref V92012803 *) has been accepted*
as a patent deposit, in accordance with
The Budapest Treaty of 1977,
with the European Collection of Animal Cell Cultures on

28 January 1992

Dr. Alan Doyle,
Curator.